

In the Specification:

On page 1, please amend the "Cross Reference to Related Applications" paragraph (lines 2-4) as follows:

This application is a divisional application of U.S. Application Serial No. 09/802,371, filed March 9, 2001, which ~~This application~~ claims the benefit of U.S. Provisional Application Serial No. 60/188,294, filed on March 10, 2000, both the contents of which are hereby incorporated by reference in their entirety.

On page 6, please amend the paragraph beginning at line 18 as follows:

Figures 4A-B show[[s]] the expression of the 26934 mRNA in various tissues and cell lines. Figure 4A shows the [[The]] level of 26934 mRNA ~~was analyzed~~ in the following tissues from left to right: artery normal; aorta diseased; vein normal; coronary SMC (smooth muscle cells); HUVEC (human umbilical vein endothelial cells); hemangioma; heart normal; heart CHF; kidney; skeletal muscle; adipose normal; pancreas; primary osteoblasts; osteoclasts (differentiated); skin normal; spinal cord normal; brain cortex normal; brain hypothalamus normal; nerve; DRG (dorsal root ganglion); breasts normal; breast tumor; ovary normal; ovary tumor. [[;]] Figure 4B shows the level of 26934 mRNA in the following tissues from left to right: prostate normal; prostate tumor; salivary glands; colon normal; colon tumor; lung normal; lung tumor; lung COPD (chronic obstructive pulmonary disease); colon IBD (inflammatory bowel disease); liver normal; liver fibrosis; spleen normal; tonsil; tonsil normal; lymph node normal; small intestine normal; macrophages; synovium; BM-MNC (bone marrow – mononuclear cells); activated PBMC (peripheral blood mononuclear cells) (resting); neutrophils; megakaryocytes; and erythroid.

On page 7, please amend the paragraph beginning at line 1 as follows:

Figures 5A-B show[[s]] the expression of the 26934 mRNA in various tissues and cell lines. Figure 5A shows the [[The]] level of the 26934 mRNA ~~was analyzed~~ in the following tissues from left to right: normal breast (columns 1-3); tumorous breast tissue (columns 4-9); lymph node (breast met) (column 10); lung (breast met) (column 11); ovary normal (columns 12-

13); tumorous ovary (columns 14-18); normal lung (columns 19-21); tumorous lung (columns 22-27).Figure 5B shows the level of 26934 mRNA in the following tissues from left to right: normal colon (columns 28-30); tumorous colon (columns 31-34); colon-liver metastasis (columns 35-36); normal liver (column 37); cervix squamous CC (columns 38-39); HMVEC (columns 40-41); normal prostate (columns 42-43); and tumorous prostate (columns 44-45).

On page 7, please amend the paragraph beginning at line 26 as follows:

Figures 10A-B summarize the expression levels of the 26934 mRNA in various ovarian cell lines. Figure 10A shows the expression levels of the 26934 mRNA as follows from left to right: SKOV-3 + GF (columns 1-8); SKOV-3/Var + GF (columns 9-16); and various cell lines (columns 17-20). Figure 10B shows the expression levels of the 26934 mRNA as follows from right to left: various cell lines (columns 1-7); HEY + Ser cMyc model (columns 8-13); and NOE vs. Ascites (columns 14-17).

On pages 22 and 23, please amend the paragraph beginning at line 26 of page 22 as follows:

The cytidine deaminase-like gene, clone 26934, was identified in a primary osteoblast cDNA library. Clone 26934 encodes an mRNA transcript having the corresponding cDNA set forth in SEQ ID NO:1. This transcript has a 1020 nucleotide open reading frame (nucleotides 147-1,167 of SEQ ID NO:1), which encodes a 339 amino acid protein (SEQ ID NO:2). An analysis of the full-length 26934 polypeptide predicts that the N-terminal 54 amino acids represent a signal peptide. A transmembrane segment from amino acids (aa) 279-299 was predicted by MEMSAT. Transmembrane segments were also predicted from aa 133-150 and from 226-243 of the presumed mature peptide sequence. Prosite program analysis was used to predict various sites within the 26934 protein. An N-glycosylation site was predicted at aa 311-314. Protein kinase C phosphorylation sites were predicted at aa 12-14, 58-60, 80-82, 130-132, and 207-209. Casein kinase II phosphorylation sites were predicted at aa 104-107, 165-168, 219-222, 246-249, and 301-304. N-myristoylation sites were predicted at aa 5-10, 24-29, and 100-105. A leucine zipper motif was predicted at aa 101-122. The cytidine deaminase-like protein possesses a cytidine and deoxycytidylate deaminase zinc-binding region, from aa 80-149, as predicted by HMMer, Version 2. For general information regarding PFAM identifiers, PS

prefix and PF prefix domain identification numbers, refer to Sonnhammer *et al.* (1997) *Protein* 28:405-420 and <http://www.psc.edu/general/software/packages/pfam/pfam.html>
www.psc.edu/general/software/packages/pfam/pfam.html. Cytidine deaminase (EC 3.5.4.5) catalyzes the hydrolysis of cytidine into uridine and ammonia while deoxycytidylate deaminase (EC 3.5.4.12) hydrolyzes dCMP into dUMP. Both enzymes are known to bind zinc and to require it for their catalytic activity. These two enzymes contain a region of three conserved histidine and cysteine residues which are thought to be involved in the binding of the catalytic zinc ion. See for example, Bhattacharya *et al.* (1994) *Trends in Biochem. Sci.* 19:105-106 and Reizer *et al.* (1994) *Protein Sci.* 3:853-856. The cytidine deaminase-like protein also possesses a Hint (Hedgehog/Intein) domain C-terminal region from aa 71-91, as predicted by HMMer, Version 2 using the SMART database.

On pages 23 and 24, please amend the paragraph beginning at line 23 of page 23 as follows:

As used herein, the term "cytidine deoxycytidylate deaminase zinc-binding region domain" includes an amino acid sequence of about 1-69 amino acid residues in length and having a bit score for the alignment of the sequence to the cytidine deoxycytidylate deaminase zinc-binding region domain (HMM) of at least 8. Preferably, an cytidine deoxycytidylate deaminase zinc-binding region domain includes at least about 1 to 69 amino acids, more about 1 to 25 amino acid residues, or about 25-60 amino acids and has a bit score for the alignment of the sequence to the cytidine deoxycytidylate deaminase zinc-binding region domain (HMM) of at least 16 or greater. The cytidine deoxycytidylate deaminase zinc-binding region domain (HMM) has been assigned the PFAM Accession PDOC00702 (<http://pfam.wustl.edu/> see pfam.wustl.edu/). An alignment of the cytidine deoxycytidylate deaminase zinc-binding region domain (amino acids 80 to 149 of SEQ ID NO:2) of human cytidine deaminase-like molecule of the invention with a consensus amino acid sequence derived from a hidden Markov model is depicted in Figure 3.

On page 24, please amend the paragraph beginning at line 12 as follows:

To identify the presence of an "cytidine deoxycytidylate deaminase zinc-binding region" domain in a cytidine deaminase-like protein sequence, and make the determination that a

polypeptide or protein of interest has a particular profile, the amino acid sequence of the protein can be searched against a database of HMMs (e.g., the Pfam database, release 2.1) using the default parameters ([\[\[http://\]\]www.sanger.ac.uk/Software/Pfam/HMM_search](http://www.sanger.ac.uk/Software/Pfam/HMM_search)). For example, the hmmsf program, which is available as part of the HMMER package of search programs, is a family specific default program for MILPAT0063 and a score of 15 is the default threshold score for determining a hit. Alternatively, the threshold score for determining a hit can be lowered (e.g., to 8 bits). A description of the Pfam database can be found in Sonhammer *et al.* (1997) *Proteins* 28(3):405-420 and a detailed description of HMMs can be found, for example, in Gribskov *et al.* (1990) *Meth. Enzymol.* 183:146-159; Gribskov *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:4355-4358; Krogh *et al.* (1994) *J. Mol. Biol.* 235:1501-1531; and Stultz *et al.* (1993) *Protein Sci.* 2:305-314, the contents of which are incorporated herein by reference.

On pages 27 and 28, please amend the paragraph beginning at line 29 of page 27 as follows:

The determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In a preferred embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch (1970) *J. Mol. Biol.* 48:444-453 algorithm which has been incorporated into the GAP program in the GCG software package (available at [\[\[http://\]\]www.gcg.com](http://www.gcg.com)), using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package (available at [\[\[http://\]\]www.gcg.com](http://www.gcg.com)), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. A particularly preferred set of parameters (and the one that should be used if the practitioner is uncertain about what parameters should be applied to determine if a molecule is within a sequence identity or homology limitation of the invention) is using a Blossum 62 scoring matrix with a gap open penalty of 12, a gap extend penalty of 4, and a frameshift gap penalty of 5.

On pages 28 and 29, please amend the paragraph beginning at line 13 of page 28 as follows:

The percent identity between two amino acid or nucleotide sequences can be determined using the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. USA* 87:2264, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul *et al.* (1990) *J. Mol. Biol.* 215:403. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12, to obtain nucleotide sequences homologous to cytidine deaminase-like nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3, to obtain amino acid sequences homologous to cytidine deaminase-like protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.* (1997) *Nucleic Acids Res.* 25:3389. Alternatively, PSI-Blast can be used to perform an iterated search that detects distant relationships between molecules. *See* Altschul *et al.* (1997) *supra*. When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used. *See* <http://www.ncbi.nlm.nih.gov>. Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller (1988) *CABIOS* 4:11-17. Such an algorithm is incorporated into the ALIGN program (version 2.0), which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used.

On page 41, please amend the paragraph beginning at line 12 as follows:

By "variants" is intended proteins or polypeptides having an amino acid sequence that is at least about 45%, 55%, 65%, preferably about 75%, 85%, 95%, or 98% identical to the amino acid sequence of SEQ ID NO:2. Variants also include polypeptides encoded by a nucleic acid molecule that hybridizes to the nucleic acid molecule of SEQ ID NO:1 or 3, or a complement thereof, under stringent conditions. In another embodiment, a variant of an isolated polypeptide of the present invention differs, by at least 1, but less than 5, 10, 20, 50, or 100 amino acid residues from the sequence shown in SEQ ID NO:2. If alignment is needed for this

comparison the sequences should be aligned for maximum identity. "Looped" out sequences from deletions or insertions, or mismatches, are considered differences. Such variants generally retain the functional activity of the cytidine deaminase-like proteins of the invention. Variants include polypeptides that differ in amino acid sequence due to natural allelic variation or mutagenesis.